REMARKS/ARGUMENTS

Claims 42, 44-75 are pending in the above-referenced patent application and are currently under examination. In the Office Action, claims 42, 44-61 and 63-75 remain rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Choi *et al.* (U.S. Patent No. 5,820,873). In addition, claims 42, 44-61 and 63-64, 67-75 remain rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Holland *et al.* (U.S. Patent No. 5,885,613). Finally, claim 62 remains rejected under 35 U.S.C. § 103 as allegedly being obvious over Choi *et al.* For the reasons set forth herein, each of the foregoing rejections is overcome.

The Invention

Novel nucleic acid-lipid particles that are useful for *in vitro* or *in vivo* gene transfer are provided by the present invention. The particles can be formed using either detergent dialysis methods or methods that utilize organic solvents. Upon removal of a solubilizing component (*i.e.*, the detergent or the organic solvent), the nucleic acid-lipid complexes form particles, wherein the nucleic acid is encapsulated in the lipid, is serum-stable and is protected from nuclease degradation.

Rejections Under 35 U.S.C. § 102(e) Over Choi et al. and Holland et al.

Claims 42, 44-61 and 63-75 remain rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5, 820,873 ("Choi *et al.*"). In addition, claims 42, 44-61, 63-64 and 67-75 remain rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,885,613 ("Holland *et al.*"). In view of the following remarks, Applicants respectfully traverse these rejections.

> To anticipate a claim, a reference must disclose each and every element of the challenged claim and must enable one skilled in the art to make the anticipated subject matter.

See, *PPG Industries Inc. v.* Guardian *Industries Corp.*, 37 USPQ2d.

Independent claim 42, as previously amended, recites: "a nucleic acid-lipid particle comprising a cationic lipid, a conjugated lipid that inhibits aggregation of particles, and a nucleic acid, wherein the nucleic acid ***is encapsulated in the lipid*** of said particle and is resistant

in aqueous solution to degradation with a nuclease. In addition, independent claim 69, as previously amended, recites: "a pharmaceutical composition comprising a nucleic acid-lipid particle and a pharmaceutically acceptable carrier, said nucleic acid-lipid particle comprising a cationic lipid, a conjugated lipid that inhibits aggregation of particles, and a nucleic acid, wherein said nucleic acid ***is encapsulated in the lipid*** of said particle and is resistant in aqueous solution to degradation with a nuclease."

As stated on page 4, lines 29-31, of the specification, the nucleic acid-lipid particles of the present invention are constructed in a way such that upon removal of a solubilizing component (*i.e.*, the detergent or the organic solvent depending on which methods is employed), the ***nucleic acid is encapsulated in the lipid and becomes protected from nuclease degradation***. The nucleic acid-lipid particles thus formed are suitable, *inter alia*, for use in intravenous nucleic acid transfer as they are stable in circulation, of a size required for pharmacodynamic behavior resulting in access to extravascular sites, and target cell populations.

In the Office Action, the Examiner maintains that the prior art compositions, *i.e.*, the compositions of Choi *et al.* and Holland *et al.*, "meet the structural limitations of the claimed compositions and are therefore presumed to have the same functional properties as Applicants' claimed compositions" (*see*, page 3 of the Office Action). Applicants respectfully ***disagree*** and, in doing so, submit concurrently herewith a ***third*** declaration, pursuant to 37 C.F.R. § 1.132, by one of skill in the art that unequivocally establishes that the compositions of Choi *et al.* and Holland *et al.* do ***not*** meet the structural limitations of the presently claimed compositions.

More particularly, in support of this position, Applicants submit concurrently herewith a 37 C.F.R. § 1.132 Declaration of Ian MacLachlan, Ph.D. that unequivocally establishes that the compositions of Choi *et al.* and Holland *et al.* do ***not*** meet the structural limitations of the presently claimed compositions because the compositions of Choi *et al.* and Holland *et al.* are ***not*** nucleic acid-lipid particles, wherein the nucleic acid component is encapsulated in the lipid component and is resistant in aqueous solution to degradation with a nuclease. The facts set forth in Dr. MacLachlan's declaration establish the following:

1. In Dr. MacLachlan's opinion, the loading/encapsulation methods disclosed in Choi *et al.* (*see*, *e.g.*, Examples 9 and 10) are useful for loading small molecules (*e.g.*, vinca

alkaloids, *etc.*) into liposomes, but are ***not*** useful for loading nucleic acids (*e.g.*, oligonucleotides, plasmid DNA, *etc.*) into liposomes because nucleic acids do ***not*** readily cross intact lipid membranes. As such, in Dr. MacLachlan's opinion, if one were to use the loading/encapsulation methods disclosed in Choi *et al.* and were to add external plasmid DNA to preformed liposomes in aqueous buffer, one would ***not*** expect to see any entrapment of the plasmid DNA in the liposomes. Again, in Dr. MacLachlan's opinion, this is because nucleic acids do not readily cross intact lipid membranes.

2. In Dr. MacLachlan's opinion, when Choi *et al.* state that cationic carriers of DNA can be improved through the addition of PEG lipids, such as the PEG-ceramide conjugates disclosed and claimed therein, Choi *et al.* are referring to the preformed cationic liposome carriers that are then complexed with DNA to form lipoplexes as described above. In fact, according to Dr. MacLachlan, the examples provided in Choi *et al.* that are directed to such preformed cationic liposomes demonstrate that aggregation of the cationic liposomes alone (no DNA) in the presence of serum (most serum proteins carry a net negative charge) can be inhibited if the liposomes contain a PEG-ceramide conjugate. Thus, in Dr. MacLachlan's opinion, these teachings of Choi *et al.* are directed to forming nucleic acid-cationic liposome ***complexes***, which are structurally and functionally ***different*** from the presently claimed nucleic acid-lipid particles, wherein the nucleic acid component is encapsulated in the lipid component and is resistant in aqueous solution to degradation with a nuclease.

3. In Dr. MacLachlan's opinion, the teachings provided in Holland *et al.* directed to the delivery of nucleic acids are essentially the ***same*** as those provided in Choi *et al.* (*see*, column 12, lines 14-26 of Holland *et al.*). Moreover, in Dr. MacLachlan's opinion, as with Choi *et al.*, the teachings of Holland *et al.* are directed to forming nucleic acid-cationic liposome ***complexes***, which are structurally and functionally ***different*** from the presently claimed nucleic acid-lipid particles, wherein the nucleic acid component is encapsulated in the lipid component and is resistant in aqueous solution to degradation with a nuclease.

4. In Dr. MacLachlan's opinion, as of the filing date of the Choi *et al.* and Holland *et al.* patents *i.e.*, 1994-1995, the state-of-the-art was to prepare cationic liposomes and, then, to complex the preformed cationic liposomes with DNA in an aqueous solution to form DNA-

cationic liposome complexes (*i.e.*, lipoplexes). Given that DNA does not readily cross lipid membranes and that the cationic lipids present in the external membrane of the vesicles would electrostatically interact with the negatively charged DNA, it is Dr. MacLachlan's opinion that the mixing of DNA with preformed cationic liposomes in aqueous solution as is taught in Choi *et al.* and Holland *et al.* does ***not*** result in entrapment of DNA within the internal, aqueous space of the liposomes. Moreover, in Dr. MacLachlan's opinion, the lipoplexes formed by the methods of Choi *et al.* and Holland *et al.* are ill-defined, are only partially protected from nucleases, are heterogeneous in size and are rapidly cleared from the circulation.

5. In Dr. MacLachlan's opinion, in contrast to the teachings of Choi *et al.* and Holland *et al.*, the present invention provides novel methods by which nucleic acids (*e.g.*, oligonucleotides, plasmid DNA, *etc.*) are entrapped, *i.e.*, encapsulated, within individual cationic liposomes that include a conjugated lipid, such as a PEG-lipid conjugate. As explained in the specification and as set forth in the presently pending claims, the PEG-lipid conjugate prevents aggregation of the particles during formation, thereby resulting in nucleic acid-lipid particles of a homogeneous and defined size containing nucleic acid that is fully encapsulated in the lipid bilayer such that the nucleic acid is completely protected from nuclease degradation. In Dr. MacLachlan's opinion, such methods of the present invention result in compositions that are structurally ***different*** from the compositions of Choi *et al.* and Holland *et al.* because nucleic acid-lipid particles made using the methods of the present invention, comprise a nucleic acid component that is encapsulated in the lipid component and is resistant in aqueous solution to degradation with a nuclease. As stated by Dr. MacLachlan, this is in stark contrast to the lipoplexes (*i.e.*, complexes) that would be formed based on the cationic liposomes of Choi *et al.* and Holland *et al.* Dr. MacLachlan's declaration provides a number of publications that establish the structural differences between the presently claimed nucleic acid-lipid particles and the prior art lipoplexes.

6. To further demonstrate that the loading/encapsulation methods of Choi *et al.* and Holland *et al.* do ***not*** produce the presently claimed nucleic acid-lipid particles, Dr. MacLachlan provides in his declaration the results of a series of experiments that were carried our using the methods of Choi *et al.* and Holland *et al.* In carrying out such experiments, the following was results were obtained: (1) plasmid encapsulation was extremely inefficient at both of the nucleic

acid:lipid ratios (*i.e.*, as low as 7% and at best only 15%) examined; (2) at least 98% of the plasmid DNA was lost on the extrusion filters; and (3) particle sizes for all of these extruded samples were all considerably larger than 100 nm (*see*, Exhibit D of Dr. MacLachlan's Declaration). In Dr. MacLachlan's opinion, these results unequivocally demonstrate that the loading/encapsulation methods described in Choi *et al.* and Holland *et al.* do ***not*** produce liposomes that encapsulate plasmid DNA, *i.e.*, nucleic acid-lipid particles wherein the nucleic acid is encapsulated in the lipid portion such that it is resistant in aqueous solution to degradation with a nuclease. As such, it is Dr. MacLachlan's opinion the compositions of Choi *et al.* and Holland *et al.* are structurally ***different*** from the presently claimed compositions.

7. In view of the foregoing, Dr. MacLachlan concludes in his declaration that ***neither*** the Choi *et al.* patent nor the Holland *et al.* patent teach (or even suggest) the nucleic acid-lipid particles recited in claims 42, 44-61 and 63-75 because ***neither*** Choi *et al.* nor Holland *et al.* teach (or even suggest) (1) nucleic acid-lipid particles, wherein the nucleic acid in the nucleic acid-lipid particles is encapsulated in the lipid portion and therefore is resistant in aqueous solution to degradation with a nuclease, or (2) methods for making such nucleic acid-lipid particles. Moreover, it is Dr. MacLachlan's opinion that the additional experiments provided in his declaration unequivocally demonstrate that the loading/encapsulation methods described in Choi *et al.* and Holland *et al.* do ***not*** lead to the presently claimed nucleic acid-lipid particles, wherein the nucleic acid is encapsulated in the lipid and is resistant in aqueous solution to degradation with a nuclease.

In view of the presently submitted MacLachlan Declaration, the previously submitted Hope Declaration and the previously submitted Semple Declaration, Applicants respectfully submit that Choi *et al.* and Holland *et al.*, which disclose methods for preparing and loading classical (or traditional) liposomes and methods for preparing nucleic acid-cationic liposome complexes, do ***not*** teach the nucleic acid-lipid particles of the present invention, wherein the nucleic acid in the nucleic acid-lipid particles is ***encapsulated in the lipid*** and is ***resistant in aqueous solution to degradation with a nuclease*** or methods for making such nucleic acid-lipid particles. Because Choi *et al.* and Holland *et al.* do ***not*** disclose each and every element of the claimed invention, they cannot form the basis of proper anticipation

rejections. Accordingly, the anticipation rejections under 35 U.S.C. § 102(e) over Choi *et al.* and Holland *et al.* are improper and should be withdrawn.

Rejection Under 35 U.S.C. § 103(a) Over Choi et al.

Claim 62 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5, 820,873 ("Choi *et al.*"). In view of the following remarks, Applicants respectfully traverse the rejection.

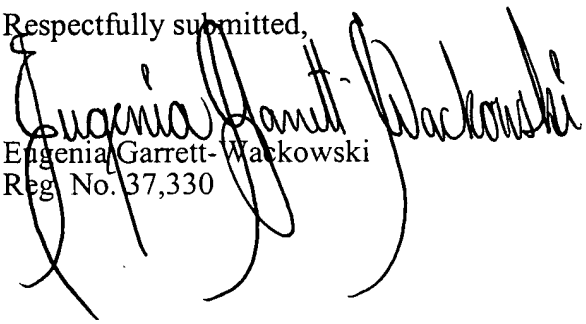
As explained above in connection with the § 102(e) rejections, Choi *et al.* do ***not*** teach (or suggest) the nucleic acid-lipid particles of the present invention, wherein the nucleic acid in the nucleic acid-lipid particles is ***encapsulated in the lipid*** and is ***resistant in aqueous solution to degradation with a nuclease*** or methods for making such nucleic acid-lipid particles. Because Choi *et al.* do ***not*** teach or suggest the presently claimed nucleic acid-lipid particles, Choi *et al.* do not teach or suggest the nucleic acid-lipid particles of claim 62, wherein the nucleic acid is a ribozyme. Accordingly, the obviousness rejection under 35 U.S.C. § 103(a) over Choi *et al.* is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 925-472-5000.

Respectfully submitted,



Eugenia Garrett-Wackowski
Reg. No. 37,330

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
EGW:lls
60456545 v1